Center for Stem Cell Biology and Regenerative Medicine

Division of Stem Cell Aging Medicine
幹細胞加齢医学分野

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Stem cell systems play fundamental roles in sustaining tissue turnover and homeostasis. Our goal is to understand the mechanisms of tissue aging and cancer development in mammals and to apply that knowledge to develop strategies to resist against tissue/organ aging, cancer development and other relevant diseases associated with aging. We further aim to apply this knowledge to drug discovery and the prevention and treatment of age-associated diseases.

1. DNA damage types and cell signaling that cause hair graying and hair thinning

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All living things experience an increase in entropy, manifested as a loss of genetic and epigenetic information. In yeast, epigenetic information is lost over time due to the relocalization of chromatin-modifying proteins to DNA breaks, causing cells to lose their identity, a hallmark of yeast aging. Using a DNA damage inducing model named "ICE", we found that the induction of DNA double strand breaks (DSBs) with faithful DNA repair advances the expression of aging phenotypes with epigenetic changes. Importantly, DNA damage foci are relatively frequently found in somatic stem cells in the skin during physiological aging. To study the fate and dynamics of DNA-damaged stem cells in tissues and the resultant impact in the expression of aging phenotypes, we first focused on the melanocyte lineage and traced the fate of melanocyte stem cells which acquired DNA DSBs and demonstrated that those cells disappear from the niche, causing the loss of mature melanocytes for hair pigmentation. This is consistent with our previous report in which we demonstrated that genotoxic stress abrogates renewal of melanocyte stem cells by triggering their ectopic differentiation (Inomata K et al. Cell, 2009). The aberrant differentiation and the resultant loss of the cell lineage in tissues may partially explain the age-associated loss of lineage-specific epigenetic information in ICE mice. More than that, the fact underlie the fact that cell components in tissues are being replaced through stem cell differentiation and their eventual depletion. We are currently testing whether the selective induction of DNA double strand breaks in melanocyte stem cells similarly causes hair graying and whether it has some beneficial effects in suppressing melanoma development from the skin. Similarly, we are testing whether DNA DSBs in hair follicle stem cells promotes hair thinning and searching for chemicals that can prevent stem cell loss by DNA DSBs.

2. Fate tracing of DNA-damaged hair follicle stem cells and their seno-differentiation clearance out of the niche

Miranda-Salmeron M, Matsumura H, Muroyama Y, Kato T, Higa M, Tan L, Kawamura Y, Nanba D, Mohri Y, and Nishimura EK.

Hair follicles, mammalian mini-organs that grow hair, miniaturize during aging, leading to hair thining and loss. In the event of severe genotoxicity such as DNA double-strand breaks (DSBs), stem cells are largely believed to choose between cell death (apoptosis) or irreversible cell cycle arrest (senescence) to prevent further damage to neighboring healthy cells and tissues. Accumulation of these senescent cells across organs has been implicated in disease and aging-related morbidities such as cancer. However, the exact fate and dynamics of sublethally damaged cells in tissues during aging/chemotherapy and the development of alopecia - and where exactly senescent cells exist in tissues are still largely unknown because of the lack of any single perfect marker of senescent cells. Previous work from our group demonstrated that various stem cells in the skin will aberrantly commit to differentiation in response to DNA damage by abrogating their self-renewal capabilities to discard unfit/stressed/aged stem cells. We are testing the unique hypothesis that the tissue youth is achieved through rapid, dynamic clearance of DNA-damaged cells out of the epithelia as a robust genomic quality control mechanism. We are evaluating a combination of recently devised mouse lines that can induce DSBs in a small number of stem cells to visualize and trace the exact fate, senescent state, and dynamics of those individual cells in epithelial tissue such as the hair follicle. Upon hair follicle stem cell (HFSC) activation, DNA-damaged cells were observed at the epidermal level, hinting to their transdermal exit out of the niche. Remarkably, while DNA damaged HFSCs exhibited gH2AX foci, SAβ-galactosidase activity nor p16 expression was not significantly increased in such cells. We are in the process of characterizing the identity of those DNA-damaged HFSCs and their fate switching in the HFSC niche that leads to hair follicle miniaturization and hair loss. Taken together, our findings demonstrate a tissue-autonomous mechanism within the hair follicle niche that can effectively discard DNA-damaged cells.

3. Dynamic stem cell selection safeguards the genomic integrity of the epidermis

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Maintaining genomic integrity and stability is crucial for life; yet, no tissue-driven mechanism that robustly safeguards the epithelial genome has been discovered. Epidermal stem cells (EpiSCs) continuously replenish the stratified layers of keratinocytes that protect organisms against various environmental stresses. To study the dynamics of DNA-damaged cells in tissues, we devised an in vivo fate tracing system for EpiSCs with DNA double-strand breaks (DSBs) and demonstrated that those cells exit from their niches. Gene expression profiling of EpiSCs with DSBs reveals that DNA damage response (DDR)-p53-Notch/p21 axis is specifically induced in EpiSCs with DSBs. Stem cell fate analysis showed that the clearance of EpiSCs with DSBs is caused by selective differentiation and delamination through the DNA damage response (DDR)-p53-Notch/p21 axis, with the downregulation of ITGB1. Moreover, concomitant enhancement of symmetric cell divisions of surrounding stem cells indicates that the selective elimination of cells with DSBs is coupled with the augmented clonal expansion of intact stem cells. These data collectively demonstrate that tissue autonomy through the dynamic coupling of cell-autonomous and non-cell-autonomous mechanisms coordinately maintains the genomic quality of the epidermis. We are currently testing the stem cell elimination process is mediated by cell competition mechanisms and also whether the phenomenon has any correlation with systemic aging.

Publications

1. Yang JH, Hayano M, Griffin PT, Amorim JA, Bonkowski MS, Apostolides JK, Salfati EL, Blanchette M, Munding EM, Bhakta M, Chew YC, Guo W, Yang X, Maybury-Lewis S, Tian X, Ross JM, Coppotelli G, Meer MV, Rogers-Hammond R, Vera DL, Lu YR, Pippin JW, Creswell ML, Dou Z, Xu C, Mitchell SJ, Das A, O'Connell BL, Thakur S, Kane AE, Su Q, Mohri Y, Nishimura EK, Schaevitz L, Garg N, Balta AM, Rego MA, Gregory-Ksander M, Jakobs TC, Zhong L, Wakimoto H, El Andari J, Grimm D, Mostoslavsky R, Wagers AJ, Tsubota K, Bonasera SJ, Palmeira CM, Seidman JG, Seidman CE, Wolf NS, Kreiling JA, Sedivy JM, Murphy GF, Green RE, Garcia BA, Berger SL, Oberdoerffer P, Shankland SJ, Gladyshev VN, Ksander BR, Pfenning AR, Rajman LA, Sinclair DA. Loss of epigenetic information as a cause of mammalian aging. Cell. 186(2): 305-326, 2023